

Serial No. 10/606,422  
Reply and Amendment dated Feb. 10, 2006  
Responding to Office Action dated Aug. 10, 2005

Docket No. ORT-1222 USA DIV

**Amendments to the Claims**

Amendments to the claims are made in the Listing of Claims beginning on page 3 of this paper.

**Remarks**

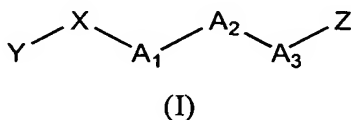
Remarks begin on page 16 of this paper.

### Listing of Claims

Claims 1-26 (Canceled)

27. (New) A method of inhibiting platelet aggregation in a subject in need thereof comprising the steps of:

- a) selecting a thrombin receptor antagonist compound of Formula I:



wherein

A<sub>1</sub> is an amino acid residue selected from the group consisting of cyclohexylalanine, Leu, Ile, Arg, Lys, Phe, substituted Phe, Tyr, and Trp;

A<sub>2</sub> is an amino acid residue selected from the group consisting of Lys, Orn, Arg, and homo Arg;

A<sub>3</sub> is an amino acid residue selected from the group consisting of Phe, substituted Phe, homo Phe, Tyr, Trp, phenylglycine, 2-thienylalanine, 3-thienylalanine, cyclohexylalanine, Leu, Ile, Asn, Gln, Arg, homo Arg, Orn, and Lys;

X is CO, CS, or SO<sub>2</sub>;

Y is selected from the group consisting of aryl, substituted aryl, heterocycloalkyl, substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heteroarylethylenyl, substituted heteroarylethylenyl, arylacrylamidoheteroaryl, substituted arylacrylamidoheteroaryl, heteroarylacrylamidoheteroaryl, and substituted heteroarylacrylamidoheteroaryl, provided that Y is not pyrrolidinyl, phenyl, or 2-aminophenyl;

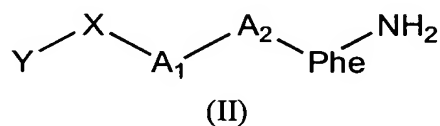
Z is NH<sub>2</sub>, NH-alkyl, NH-aralkyl, or Arg-NH<sub>2</sub>; and

wherein all amino acids are of the L configuration;

and any pharmaceutically acceptable salt thereof; and

b) administering to the subject a therapeutically effective amount of said compound.

28. (New) A method of Claim 27 wherein said compound is selected from a compound of Formula II:



wherein:

Y	A <sub>1</sub>	A <sub>2</sub>	X
5-( <i>o</i> -Cl-cinnamamido)triazol-3-yl	Cha	Arg	CO
5-(Thien-2-ylacrylamido) triazol-3-yl	Cha	Arg	CO
5-(Cinnamamido)triazol-3-yl	Cha	Arg	CO
5-( $\alpha$ -Me-cinnamamido) triazol-3-yl	Cha	Arg	CO
5-( $\alpha$ -Ph-cinnamamido) triazol-3-yl	Cha	Arg	CO
6-Cinnamamidopyridin-3-yl	Cha	Arg	CO
5-Cl, 3-Me-benzothiophen-2-yl	Cha	Arg	SO <sub>2</sub>

Y	A <sub>1</sub>	A <sub>2</sub>	X
5-(p-F-cinnamamido) triazol-3-yl	Cha	Arg	CO
Benzothiophen-2-yl	Cha	Arg	CO
1-naphthyl	Cha	Arg	SO <sub>2</sub>
2-naphthyl	Cha	Arg	SO <sub>2</sub>

29. (New) A method of Claim 27 wherein said compound is selected from the group consisting essentially of:

[5-cinnamamidotriazol-3-yl]carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide;

(6-Cinnamamidopyridin-3-yl)carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide; and

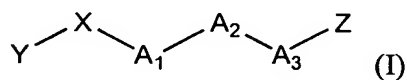
(5-Chloro-3-methyl-benzothiophen-2-yl)carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide.

30. (New) The method of Claim 27, wherein the therapeutically effective amount of the compound is about 0.1 to about 300 mg/kg/day.

31. (New) The method of Claim 30, wherein the therapeutically effective amount of the compound is about 1 to about 50 mg/kg/day.

32. (New) A method of inducing platelet aggregation in a subject in need thereof comprising the steps of:

a) selecting a thrombin receptor agonist compound of Formula I:



wherein

A<sub>1</sub> is an amino acid residue selected from the group consisting of cyclohexylalanine, Leu, Ile, Arg, Lys, Phe, substituted Phe, Tyr, and Trp;

A<sub>2</sub> is an amino acid residue selected from the group consisting of Lys, Orn, Arg, and homo Arg;

A<sub>3</sub> is an amino acid residue selected from the group consisting of Phe, substituted Phe, homo Phe, Tyr, Trp, phenylglycine, 2-thienylalanine, 3-thienylalanine, cyclohexylalanine, Leu, Ile, Asn, Gln, Arg, homo Arg, Orn, and Lys;

X is CO, CS, or SO<sub>2</sub>;

Y is selected from the group consisting of aryl, substituted aryl, heterocycloalkyl, substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heteroarylethylenyl, substituted heteroarylethylenyl, arylacrylamidoheteroaryl, substituted arylacrylamidoheteroaryl, heteroarylacrylamidoheteroaryl, and substituted heteroarylacrylamidoheteroaryl, provided that Y is not pyrrolidinyl, phenyl, or 2-aminophenyl;

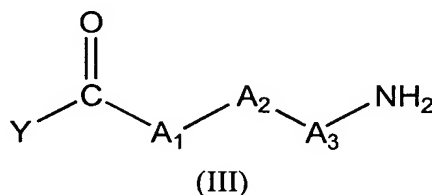
Z is NH<sub>2</sub>, NH-alkyl, NH-aralkyl, or Arg-NH<sub>2</sub>; and

wherein all amino acids are of the L configuration;

and any pharmaceutically acceptable salt thereof; and

b) administering to the subject a therapeutically effective amount of said compound.

33. (New) A method of Claim 32 wherein said compound is selected from a compound of Formula III:



wherein:

Y	A <sub>1</sub>	A <sub>2</sub>	A <sub>3</sub>
5-H <sub>2</sub> N-1,2,4-triazol-3-yl	Cha	Arg	Phe
5-Bromopyridin-3-yl	Cha	Arg	Phe
2-Chromonyl	Cha	Arg	Phe
5-( $\alpha$ -Me-cinnamamido)triazol-3-yl	Cha	Arg	Phe
5-Naphthylacrylamidotriazol-3-yl	Cha	Arg	Phe
Quinoxalin-2-yl	Cha	Arg	Phe
5-( <i>o</i> -Cl-cinnamamido)triazol-3-yl	Cha	Arg	Phe
6-Aminopyridin-3-yl	Cha	Arg	Phe
5-H <sub>2</sub> N-1,2,4-triazol-3-yl	Cha	Arg	Phe-Arg
Thiadiazol-4-yl	Cha	Arg	Phe
5-(2,3-diMeO-cinnamamido)triazol-3-yl	Cha	Arg	Phe
5-( $\alpha$ -F-cinnamamido)triazol-3-yl	Cha	Arg	Phe
5-( <i>m</i> -NO <sub>2</sub> -cinnamamido)triazol-3-yl	Cha	Arg	Phe
5-( <i>o</i> -NO <sub>2</sub> -cinnamamido)triazol-3-yl	Cha	Arg	Phe
Pyridin-3-yl	Cha	Arg	Phe

Y	A <sub>1</sub>	A <sub>2</sub>	A <sub>3</sub>
5-( <i>m</i> -Cl-cinnamamido)triazol-3-yl	Cha	Arg	Phe
5-H <sub>2</sub> N-1,2,4-triazol-3-yl	Phe	Arg	Phe
5-H <sub>2</sub> N-1,2,4-triazol-3-yl	Cha	Lys	Phe
5-H <sub>2</sub> N-1,2,4-triazol-3-yl	Cha	Arg	Cha
5-H <sub>2</sub> N-1,2,4-triazol-3-yl	Cha	Arg	Phgly
5-(thiophen-2-ylacrylamido)triazol-3-yl	Cha	Arg	Phe
3-H <sub>2</sub> N-pyrazin-2-yl	Cha	Arg	Phe
trans 2-(3-pyridyl)ethylenyl	Cha	Arg	Phe
5-( <i>p</i> -MeO-cinnamamido)triazol-3-yl	Cha	Arg	Phe
5-( <i>p</i> -CN-cinnamamido)triazol-3-yl	Cha	Arg	Phe
5-( <i>p</i> -F-cinnamamido)triazol-3-yl	Cha	Arg	Phe
2-H <sub>2</sub> N-pyridin-3-yl	Cha	Arg	Phe
5-H <sub>2</sub> N-1,2,4-triazol-3-yl	Cha	Arg	Tyr
5-H <sub>2</sub> N-1,2,4-triazol-3-yl	Cha	Arg	2-Thala
Pyridin-2-yl	Cha	Arg	Phe
5-( <i>p</i> -Phenyl-cinnamamido)triazol-3-yl	Cha	Arg	Phe

Y	A <sub>1</sub>	A <sub>2</sub>	A <sub>3</sub>
N-( <i>p</i> -F-phenylalanyl)-piperidin-3-yl	Cha	Arg	Phe
5-(Cinnamamido)triazol-3-yl	Cha	Arg	Phe
5-( $\alpha$ -phenyl-cinnamamido)triazol-3-yl	Cha	Arg	Phe
3-aminophenyl	Cha	Arg	Phe
1-biphenyl	Cha	Arg	Phe
2-biphenylenyl	Cha	Arg	Phe
benzimidazol-5-yl	Cha	Arg	Phe

34. (New) A method of Claim 32 wherein said compound is selected from the group consisting essentially of:

(5-Bromopyridin-3-yl)carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide;

2-Chromonylcarbonyl-cyclohexylalanyl-arginyl-phenylalanineamide;

(5-Aminotriazol-3-yl)carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide;

[5-( $\alpha$ -Methyl)cinnamamidotriazol-3-yl]carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide;

{5-[3-(1-Naphthyl)acrylamido]triazol-3-yl}carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide;

[Quinoxalin-2-yl]carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide;

[5-(*o*-Chlorocinnamamido)triazol-3-yl]carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide;

(6-Aminopyridin-3-yl)carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide;

(5-Aminotriazol-3-yl)carbonyl-phenylalanyl-arginyl-phenylalanyl-arginineamide;

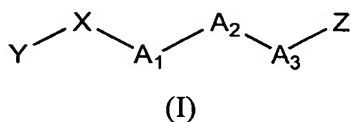
(5-Aminotriazol-3-yl)carbonyl-cyclohexylalanyl-lysiny-phenylalanineamide; and

{5-[3-(2-Thienyl)acrylamido]triazol-3-yl} carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide.

35. (New) The method of Claim 32, wherein the therapeutically effective amount of the compound is about 0.1 to about 300 mg/kg/day.

36. (New) The method of Claim 35, wherein the therapeutically effective amount of the compound is about 1 to about 50 mg/kg/day.

37. (New) A method of treating a platelet-mediated thrombotic disorder selected from the group consisting of myocardial infarction, stroke, angina, and ischemic attacks in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Formula I:



wherein

A<sub>1</sub> is an amino acid residue selected from the group consisting of cyclohexylalanine, Leu, Ile, Arg, Lys, Phe, substituted Phe, Tyr, and Trp;

A<sub>2</sub> is an amino acid residue selected from the group consisting of Lys, Orn, Arg, and homo Arg;

A<sub>3</sub> is an amino acid residue selected from the group consisting of Phe, substituted Phe, homo Phe, Tyr, Trp, phenylglycine, 2-thienylalanine, 3-thienylalanine, cyclohexylalanine, Leu, Ile, Asn, Gln, Arg, homo Arg, Orn, and Lys;

X is CO, CS, or SO<sub>2</sub>;

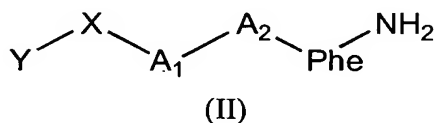
Y is selected from the group consisting of aryl, substituted aryl, heterocycloalkyl, substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heteroarylethylenyl, substituted heteroarylethylenyl, arylacrylamidoheteroaryl, substituted arylacrylamidoheteroaryl, heteroarylacrylamidoheteroaryl, and substituted heteroarylacrylamidoheteroaryl, provided that Y is not pyrrolidinyl, phenyl, or 2-aminophenyl;

Z is NH<sub>2</sub>, NH-alkyl, NH-aralkyl, or Arg-NH<sub>2</sub>; and

wherein all amino acids are of the L configuration;

and any pharmaceutically acceptable salt thereof.

38. (New) A method of Claim 37 wherein said compound is selected from a compound of Formula II:



wherein:

Y	A <sub>1</sub>	A <sub>2</sub>	X
5-( <i>o</i> -Cl-cinnamamido)triazol-3-yl	Cha	Arg	CO
5-(Thien-2-ylacrylamido) triazol-3-yl	Cha	Arg	CO
5-(Cinnamamido)triazol-3-yl	Cha	Arg	CO
5-( $\alpha$ -Me-cinnamamido) triazol-3-yl	Cha	Arg	CO

Y	A <sub>1</sub>	A <sub>2</sub>	X
5-( $\alpha$ -Ph-cinnamamido) triazol-3-yl	Cha	Arg	CO
6-Cinnamamidopyridin-3-yl	Cha	Arg	CO
5-Cl, 3-Me-benzothiophen-2-yl	Cha	Arg	SO <sub>2</sub>
5-(p-F-cinnamamido) triazol-3-yl	Cha	Arg	CO
Benzothiophen-2-yl	Cha	Arg	CO
1-naphthyl	Cha	Arg	SO <sub>2</sub>
2-naphthyl	Cha	Arg	SO <sub>2</sub>

39. (New) A method of Claim 37 wherein said compound is selected from the group consisting essentially of:

[5-cinnamamidotriazol-3-yl]carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide;

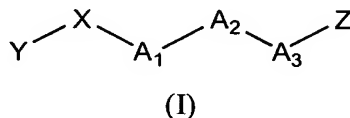
(6-Cinnamamidopyridin-3-yl)carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide; and

(5-Chloro-3-methyl-benzothiophen-2-yl)carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide.

40. (New) The method of Claim 37, wherein the therapeutically effective amount of the compound is about 0.1 to about 300 mg/kg/day.

41. (New) The method of Claim 40, wherein the therapeutically effective amount of the compound is about 1 to about 50 mg/kg/day.

42. (New) A method of treating restenosis in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Formula I:



wherein

A<sub>1</sub> is an amino acid residue selected from the group consisting of cyclohexylalanine, Leu, Ile, Arg, Lys, Phe, substituted Phe, Tyr, and Trp;

A<sub>2</sub> is an amino acid residue selected from the group consisting of Lys, Orn, Arg, and homo Arg;

A<sub>3</sub> is an amino acid residue selected from the group consisting of Phe, substituted Phe, homo Phe, Tyr, Trp, phenylglycine, 2-thienylalanine, 3-thienylalanine, cyclohexylalanine, Leu, Ile, Asn, Gln, Arg, homo Arg, Orn, and Lys;

X is CO, CS, or SO<sub>2</sub>;

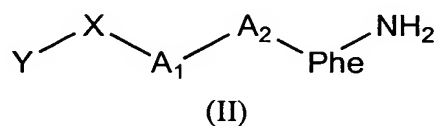
Y is selected from the group consisting of aryl, substituted aryl, heterocycloalkyl, substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heteroarylethylenyl, substituted heteroarylethylenyl, arylacrylamidoheteroaryl, substituted arylacrylamidoheteroaryl, heteroarylacrylamidoheteroaryl, and substituted heteroarylacrylamidoheteroaryl, provided that Y is not pyrrolidinyl, phenyl, or 2-aminophenyl;

Z is NH<sub>2</sub>, NH-alkyl, NH-aralkyl, or Arg-NH<sub>2</sub>; and

wherein all amino acids are of the L configuration;

and any pharmaceutically acceptable salt thereof.

43. (New) A method of Claim 42 wherein said compound is selected from a compound of Formula II:



wherein:

Y	A <sub>1</sub>	A <sub>2</sub>	X
5-( <i>o</i> -Cl-cinnamamido)triazol-3-yl	Cha	Arg	CO
5-(Thien-2-ylacrylamido) triazol-3-yl	Cha	Arg	CO
5-(Cinnamamido)triazol-3-yl	Cha	Arg	CO
5-( $\alpha$ -Me-cinnamamido) triazol-3-yl	Cha	Arg	CO
5-( $\alpha$ -Ph-cinnamamido) triazol-3-yl	Cha	Arg	CO
6-Cinnamamidopyridin-3-yl	Cha	Arg	CO
5-Cl, 3-Me-benzothiophen-2-yl	Cha	Arg	SO <sub>2</sub>
5-( <i>p</i> -F-cinnamamido) triazol-3-yl	Cha	Arg	CO
Benzothiophen-2-yl	Cha	Arg	CO
1-naphthyl	Cha	Arg	SO <sub>2</sub>

Y	A <sub>1</sub>	A <sub>2</sub>	X
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2-naphthyl	Cha	Arg	SO <sub>2</sub>	.
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44. (New) A method of Claim 42 wherein said compound is selected from the group consisting essentially of:

[5-cinnamamidotriazol-3-yl]carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide;

(6-Cinnamamidopyridin-3-yl)carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide; and

(5-Chloro-3-methyl-benzothiophen-2-yl)carbonyl-cyclohexylalanyl-arginyl-phenylalanineamide.

45. (New) The method of Claim 42, wherein the therapeutically effective amount of the compound is about 0.1 to about 300 mg/kg/day.

46. (New) The method of Claim 45, wherein the therapeutically effective amount of the compound is about 1 to about 50 mg/kg/day.